

AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A method of identifying a subject predisposed to ischemic stroke,  
~~the wherein said method including the step of comprises:~~ *= level of expression?*  
determining a rate of release of tissue plasminogen activator in a subject; and  
identifying a subject predisposed to ischemic stroke by a reduction in the rate of release of tissue  
plasminogen activator in the subject  
~~identifying a mutation in the subject that reduces the release rate of tissue plasminogen activator.~~

2. (Currently Amended) ~~[[A]]~~The method according to claim 1, wherein the ischemic stroke  
is a lacunar stroke.

3. (Currently Amended) ~~[[A]]~~The method according to ~~claims 1 or 2~~claim 130, wherein the  
mutation is located in the tissue plasminogen activator locus.

4. (Currently Amended) ~~[[A]]~~The method according to claim 3, wherein the mutation is  
located in an upstream region of the tissue plasminogen activator locus.

5. (Cancelled)

6. (Currently Amended) A method according to ~~any one of claims~~claim 3 to 5, wherein the  
mutation is located in both alleles of the tissue plasminogen activator locus.

7. (Currently Amended) ~~[[A]]~~The method according to ~~claim 6~~claim 3, wherein the mutation is a cytosine to thymine mutation at position -7351 of the upstream region of the tissue plasminogen locus.

8. (Cancelled)

9. (Currently Amended) ~~[[A]]~~The method according to ~~any one of claims 1 to 8~~claim 130, wherein the identification of the mutation includes detection of the mutation by ~~hybridisation~~ hybridization of nucleic acid isolated or derived from the subject to a reporter nucleic acid.

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see  
Klutt et al.  
pp. 6-7,  
12-13 = kits

10. (Currently Amended) A method of identifying a subject predisposed to small vessel occlusion, ~~the~~wherein said method including the step of comprises:  
determining a rate of release of tissue plasminogen activator in a subject; and  
identifying a ~~mutation in the subject that reduces the predisposed to small vessel occlusion by a~~  
reduction in the rate of release rate of tissue plasminogen activator in the subject.

11. (Currently Amended) ~~[[A]]~~The method according to claim 40132, wherein the small vessel occlusion manifests clinically as a disease or condition selected from the group consisting of:  
lacunar stroke, dementia, ischemic heart disease, ~~(including ischemic cardiomyopathy)~~, peripheral vascular disease, disseminated intravascular coagulation, small vessel vasculitis, ischemic neuropathy, ischemic retinopathy, ischemic gastropathy, ~~(including small and large bowel ischemia)~~, diffuse pulmonary embolism, and vascular impotence.

gastropathy, ~~(including small and large bowel ischemia)~~, diffuse pulmonary embolism, ~~or~~ and vascular impotence.

51-114. (Cancelled)

115. (Currently Amended) An isolated nucleic acid ~~with~~ comprising:

(i) one or more base substitutions in the sequence according to SEQ ID NO: 3, or

(ii) SEQ ID NO:4, or

(iii) a RNA equivalent of (i) or (ii); or

(iv) SEQ ID NO:3 having one or more nucleotide substitutions

(v) SEQ ID NO:4 having one or more nucleotide substitutions;

wherein the isolated nucleic acid has sequences having one or more nucleotide substitutions

are at least 80% homology homologous to SEQ. ID NO:3 or SEQ ID NO:4, or

wherein the isolated nucleic acid having one or more nucleotide substitutions hybridizes

with the complement of SEQ ID NO:3 or SEQ ID NO:4 under stringent

hybridization conditions comprising hybridization at 6xSSC at 42 °C and washing in

2xSSC at 20 °C or RNA equivalent thereof.

116-129. (Cancelled)

130. (New) The method according to claim 1, wherein said method further comprises:

determining a reduced rate of release of tissue plasminogen activator in the subject by identifying a mutation in the subject that reduces the [rate of release] of tissue plasminogen activator in the subject.

a gene in the genome of

level & expression

112, 134  
only 1  
mutation is  
disclosed in the  
spec.

The entire genome of the  
subject would have to be  
sequenced & each mutation would  
have to be confirmed as a mutation, rel.  
to some std.  
E.g. mutation would have to be  
correlated + or - w/ reduced t-PA  
expression.

131. (New) The method according to claim 1, wherein the method is used to (i) identify a subject suitable for intervention to prevent and/or treat ischemic stroke; and/or (ii) determine the risk of ischemic stroke occurring in a subject.

132. (New) The method according to claim 10, wherein said method further comprises:  
determining a reduced rate of release of tissue plasminogen activator in the subject by identifying a mutation in the subject that reduces the rate of release of tissue plasminogen activator in the subject.

133. (New) The method according to claim 10, wherein the subject having a reduced rate of release of tissue plasminogen activator is suitable for (i) intervention to prevent and/or treat ischemic stroke; and/or (ii) intervention to prevent and/or treat a small vessel occlusion; and/or (iii) intervention to prevent and/or treat a disease or condition associated with small vessel occlusion.

134. (New) The method according to claim 49, wherein the agent is monosodium [2-(6-hydroxynaphthalen-2-yl)-6-methyl-pyrimidin-4-yloxy]acetate dihydrate (JTV-926) or other bradykinin agonist.

12. (Cancelled)

13. (Currently Amended) ~~[[A]]The method according to any one of claims 10 to 12~~claim 132, wherein the mutation is located in the tissue plasminogen activator locus.

14-16. (Cancelled)

17. (Currently Amended) ~~[[A]]The method according to claim 16~~claim 132, wherein the mutation is a cytosine to thymine mutation at position -7351 of the upstream region of the tissue plasminogen locus.

18-34. (Cancelled)

35. (Currently Amended) ~~[[A]]The method according to claim 35~~claim 132, wherein the mutation is in both alleles of the tissue plasminogen activator locus.

36-37. (Cancelled)

38. (Currently Amended) ~~[[A]]The method according to any one of claims 30 to 37~~claim 132, wherein the identification of the mutation includes detection of the mutation by ~~hybridisation~~hybridization of nucleic acid isolated or derived from the subject to a reporter nucleic acid.

39. (Cancelled)

40. (Currently Amended) ~~[[A]]~~The method according to claim ~~39~~133, wherein the disease or condition is selected from the group consisting of: lacunar stroke, dementia, ischemic heart disease, ~~(including~~ ischemic cardiomyopathy), peripheral vascular disease, disseminated intravascular coagulation, small vessel vasculitis, ischemic neuropathy, ischemic retinopathy, ischemic gastropathy, ~~(including~~ small and large bowel ischemia), diffuse pulmonary embolism, ~~or~~and vascular impotence.

41-48. (Cancelled)

49. (Currently Amended) A method of treating and/or treating a disease or condition associated with small vessel occlusion in a subject, ~~the~~wherein said method ~~including the step of~~comprises:  
administering to the subject a therapeutically effective amount of an agent that increases the rate of release of tissue plasminogen activator in the subject.

50. (Currently Amended) ~~[[A]]~~The method according to claim 49, wherein the disease or condition is selected from the group consisting of: a lacunar stroke, dementia, ischemic heart disease, ~~(including~~ ischemic cardiomyopathy), peripheral vascular disease, disseminated intravascular coagulation, small vessel vasculitis, ischemic neuropathy, ischemic retinopathy, ischemic